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EXAMINER	
BAKER, A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/965,356	Applicant(s) Bernfield et al.
	Examiner Anne-Marie Baker, Ph.D.	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant's election with traverse of Group II, Claims 10-15, in Paper No. 7 is acknowledged. The traversal is on the grounds that no further searching would be required to search the Claims of Group I, since the art should be substantially the same. Applicant argues that a search for prior art relating to the Group II claims will necessarily encompass a search for prior art relating to the Group I claims. Applicant's arguments have been considered and the examination of Groups I and II have been combined.

Claims 1-15 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to a non-human transgenic animal wherein the ligand binding function of the melanocortin 4 receptor has been inactivated. Although Claim 1 does not indicate what type of binding function has been inactivated, it is assumed that the receptor loses its ability to bind to

its native ligand, apparently as a consequence of the expression of a transgene encoding a protein that binds to the melanocortin 4 receptor, thereby inactivating its capacity to bind to its ligand. Claims 2-6 are drawn to transgenic animals expressing a syndecan molecule, particularly syndecan-1, wherein the animals also have an inactive melanocortin 4 receptor as the result of the introduction of a separate transgene. Claims 7-9 are drawn to a transgene construct encoding a syndecan. Claims 10-15 are drawn to methods for screening compounds which can alter body weight.

The specification fails to provide an enabling disclosure for the preparation of any and all animals with an inactive melanocortin 4 receptor because no guidance is offered in the specification for the preparation of such animals. Claim 1 encompasses knockout animals wherein the binding site of the receptor has been mutated such that it loses its binding activity. Such animals would have had to have been prepared using homologous recombination to replace the endogenous melanocortin 4 receptor with a mutated form of the gene wherein the nucleotides encoding the ligand binding site of the receptor had been altered in such a way as to disrupt ligand binding. The specification fails to provide any guidance for any means of producing the claimed animals. First, the ligand binding site of the receptor had not been identified, and therefore the artisan would not have known what alterations would have been required to disrupt the binding function. Second, Lee et al., 1997 disclose that the identity of the native ligand remains unidentified (p. 1, lines 34-35). Third, the only means for producing such animals would have been via homologous recombination in embryonic stem cells. As noted by Bradley et al., 1992

(U), the preparation of mice harboring mutations in particular genes was possible using embryonic stem cell technology. However, the only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537 and 538). Campbell and Wilmut, 1997 (V) acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Since ES cell technology would have been required to have practiced the claimed methods, in the absence of such technology available in other species, the artisan would have been required to have exercised undue experimentation in the practice of the claimed methods in species other than mice.

The specification fails to provide an enabling disclosure in regard to the mutation contemplated in the melanocortin 4 receptor, wherein the alteration would have made the receptor inactive for ligand binding, because no exemplification of any such alterations are provided in the specification. Since the binding site of the receptor had not been identified and the ligand that binds to the receptor had also not been identified, undue experimentation would have been required for the artisan to have made mutations that would have disrupted ligand binding. In the absence of any known ligand, the artisan would not have been able to establish that the ligand binding function had in fact been inactivated.

The specification fails to provide an enabling disclosure for the use of transgenic animals having a mutated melanocortin 4 receptor gene because no particular phenotype associated with

such animals had been demonstrated. The specification does not describe any animals, not even mice, wherein the receptor gene had been mutated. Given the lack of exemplification, the effect of mutations of the type contemplated on the phenotype of the animal or mouse remains unknown. Thus, the method of screening for compounds which can alter body weight, wherein the compound is administered to the receptor-mutated transgenic animal is not enabled because the phenotype of such animals was not known. Evidence for the role of MC4-R in body weight regulation came after the priority date of the instant application. In January 1997, Huszar et al. described melanocortin 4 receptor knockout mice, wherein the MC4-R coding sequence was deleted via homologous recombination with a targeting vector in embryonic stem cells. The mice developed maturity onset obesity, as referenced in the instant specification on p. 4, lines 10-12. Furthermore, peptides mimicking melanocortins were found to bind to MC4-R and suppressed feeding when injected into the brains of normal mice (see Gura, 1997, p. 753, column 2, paragraph 3). This finding is referred to in the specification on p. 4, lines 8-9. Even had such evidence for the role of MC4-R in body weight regulation been available at the time of the instant application, the phenotype of transgenic animals of the type claimed could not have been predicted and thus a model system useful for the study of obesity and the screening of compounds to regulate body weight as claimed in the instant invention would not necessarily have been expected.

The specification fails to provide an enabling disclosure for the preparation and use of transgenic animals wherein the MC4-R gene is mutated and, additionally, the syndecan-1 gene is

integrated into the genome such that syndecan-1 is expressed from a heterologous construct, because no guidance is provided in the specification for the preparation and use of such double transgenic animals. As discussed above, phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known. Further, the combined effect resulting from the introduction of two separate transgenes is unpredictable even when the function of each gene and gene product is known and even when the interaction of the gene products with each other is also known. In this particular case, the interaction of syndecan-1 with MC4-R is unknown. Although the claims refer to the binding of syndecan-1 to MC4-R, there is no evidence either in the literature or in the specification for this interaction. Thus the model system of Claims 10-15, wherein the double transgenic animals are useful for the screening of compounds which can alter body weight would not be predicted and has not been demonstrated.

The specification fails to provide an enabling disclosure for the preparation and use of transgenic animals wherein the ligand binding function of the melanocortin 4 receptor has been inactivated as a consequence of the expression of a transgene encoding a protein that binds to the melanocortin 4 receptor, thereby inactivating its capacity to bind to its ligand. Claim 1 reads on both a receptor-mutated transgenic animal as well as on a transgenic animal carrying a transgene encoding a molecule that binds to and inactivates MC4-R. Claim 3 is drawn to the transgenic animal expressing a syndecan, wherein the syndecan binds to the melanocortin 4 receptor, thereby inactivating it. However, there is no evidence either in the literature or in the specification that a

syndecan does in fact bind to the melanocortin 4 receptor, nor is there any evidence that such binding would be expected to inactivate the ligand binding function of the receptor. As discussed above, the ligand that binds to the receptor had not been identified (see Lee et al., p. 1, lines 34-35) at the time of the instant invention. Thus, in the absence of a known ligand, the artisan would not have been able to establish that the ligand binding function had in fact been inactivate. The specification offers no guidance for determining which molecules would inactivate receptor binding and there is no demonstration that expression of any syndecan, including syndecan-1, results in inactivation of the receptor. Furthermore, Claims 10-15 presume that the transgenic animal with binding to the melanocortin 4 receptor inactivated is useful for screening compounds which can alter body weight. However, there is no demonstration in the specification for any phenotypic alteration directly related to this presumed loss of binding function. Thus, the use of such animals for the screening of body weight altering compounds is questionable.

The specification fails to provide an enabling disclosure for the transgenic animals wherein the transgene is preferentially expressed in the hypothalamus as recited in Claim 4, because there is no demonstration of preferential expression nor any mechanism known to drive this pattern of expression. Table 3 on p. 22 of the specification summarizes the tissue-specific expression of syndecan-1 in both wild-type and transgenic mice. The syndecan-1 transgenic mice exhibited increased expression of syndecan-1 in heart, kidney, pancreas, skeletal muscle, and adrenal gland compared to wild-type mice. However, data for expression in the brain as a whole and localization of expression within the brain is not included in the table. Thus, a basis for

comparison of expression in the brain with expression in other tissues is not provided. The specification (p. 23) discloses that expression of syndecan-1 was observed in the paraventricular, suprachiasmatic, lateral, dorso-medial, and arcuate nuclei of the hypothalamus, but does not indicate which other regions of the brain were tested for expression and what levels of expression were found. Since the level of expression in the brain is not given, no comparison can be made to the results of Table 3 which details the level of expression found in a variety of tissues. Therefore, it is not evident that preferential expression in the hypothalamus can be achieved in the claimed transgenic animals. Given the lack of working examples in the specification and the lack of guidance for employing a regulatory mechanism to drive expression of the transgene preferentially in the hypothalamus, one skilled in the art would have been required to have exercised undue experimentation to practice the claimed invention.

The specification fails to provide an enabling disclosure for the use of the transgene constructs of Claims 7-9, because it does not teach how to achieve hypothalamus specificity, as discussed above. As shown in Table 3, the CMV promoter/enhancer construct drives transgene expression in many tissues, including heart, kidney, pancreas, skeletal muscle, and adrenal gland. Chapman et al., 1991 report that the enhancer is active in a broad range of host cell types (p. 3979, paragraph 2). Given the lack of demonstration of hypothalamus-specific transgene expression and in the absence of any guidance regarding regulatory elements that can be used to drive hypothalamus-specific transgene expression, the artisan would have been required to have exercised undue experimentation to practice the claimed invention.

The specification fails to provide an enabling disclosure for the preparation of any transgenic animals carrying a syndecan-encoding transgene construct other than mice. The specification describes the preparation of mice expressing a transgene construct comprising a nucleic acid molecule encoding syndecan-1 operably linked to the CMV promoter/enhancer regulatory regions, wherein expression of the transgene results in mice that exhibit maturity onset obesity. Syndecans have been identified in the mouse, rat, hamster, and human. However, other animals for which syndecans have not been identified, or for which the gene for a syndecan is not known, are not enabled for the generation of transgenics that overexpress a syndecan transgene. Furthermore, phenotypic alterations resulting from the introduction of transgenes is highly unpredictable. Given the lack of any demonstration of a maturity onset obesity resulting from expression of a syndecan transgene in any animal other than the mouse and given the unpredictability of obtaining a specific phenotypic alteration as the result of the introduction of a defined transgene construct, one skilled in the art would have been required to have exercised undue experimentation to have practiced the invention in any animal other than the mouse. Thus, limitation to mice carrying the claimed transgene construct is appropriate.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 are indefinite in regard to the "transgenic animal having binding to the melanocortin 4 receptor function inactivated" because it is unclear what binding function is inactivated and to what extent binding is disrupted. The native ligand for MC4-R remains unidentified (see Lee et al., 1997, p. 1, paragraph 3). However, ectopically expressed agouti protein is known to bind to MC4-R (Lee et al., p. 5, paragraph 1).

Claims 2-5 are indefinite in regard to the animal that expresses a molecule from a construct "wherein the molecule binds to the melanocortin 4 receptor" because the transgenic animal is said to have a melanocortin 4 receptor that is inactive with regard to its binding function. Thus, the recitation of the phrase "wherein the molecule binds to the melanocortin 4 receptor" is confusing because the animal is presumed to have a receptor that cannot bind to any ligand.

Claims 4, 13, 14, and 15 are indefinite in regard to the molecule that is "expressed preferentially in the hypothalamus" because it is unclear whether the preferential expression is with regard to other areas of the brain or the whole body. For example, the transgene may be expressed in a number of tissues throughout the body and yet, within the brain, exhibit limited expression such that only particular regions of the brain express the transgene.

Claim 11 is indefinite in regard to the method of Claim 10 wherein the animal expresses a molecule that binds to the melanocortin 4 receptor because the animal of Claim 10 is presumed to

have a receptor that is inactive with regard to its binding function and thus would not be expected to bind to any ligand.

Claim 12 is indefinite in the recitation of "the method of claim 10 wherein the molecule is a syndecan" because the term "the molecule" lacks antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomsen et al., 1984 (W), Boshart et al., 1985 (X), and Saunders et al., 1996, U.S. Patent No. 5,486,599.

The claims are drawn to recombinant DNA constructs comprising a cytomegalovirus promoter including the intermediate/early enhancer and a nucleic acid molecule encoding syndecan-1, wherein the syndecan is preferentially expressed in the hypothalamus.

Thomsen et al. disclose the nucleotide sequence for the promoter of the major IE gene of human cytomegalovirus (p. 661, Figure 3). Thomsen et al. do not disclose the nucleotide sequence for the IE enhancer or syndecan-1.

Boshart et al. disclose the nucleotide sequence of the human cytomegalovirus (hCMV) enhancer region of the major IE gene (p. 523, Figure 3). The investigators also report that the hCMV enhancer shows little cell type or species preference. Boshart et al. do not disclose the nucleotide sequence for syndecan-1.

Saunders et al., in U.S. Pat. No. 5,486,599, disclose the nucleotide and amino acid sequence of murine syndecan-1 (SEQ ID NO: 1).

Since analysis of gene function and gene expression typically requires the use of recombinant constructs for controlled expression of known gene sequences, one would have been motivated to place the murine syndecan-1 gene under control of a ubiquitous promoter such that the gene would be expressed in cells transformed with the construct. One would have anticipated a reasonable expectation of success because only standard molecular biology techniques are required to make the construct and the structure and function of the CMV promoter are well-known. Furthermore, the CMV promoter has frequently been used to drive expression of exogenous genes because promoter/enhancer activity is known to be very strong relative to other known promoters (see Chapman et al., 1991, column 1, paragraph 2). Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made a gene construct wherein the CMV promoter/enhancer was used to drive expression of syndecan-1 or any other known syndecan gene.

One would have been motivated to have combined the teachings of Thomsen et al., Boshart et al., and Saunders et al. in order to express syndecan-1 in a transformed cell line for analysis of the function of the exogenously expressed protein.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Applicant is advised that the disclosed transgenic mouse with a syndecan-1 gene operably linked to regulatory regions that drive expression of the transgene such that the mouse exhibits maturity onset obesity is enabled by the specification but not expressly claimed as such. The assay for screening compounds which can alter body weight is also enabled for the same scope as the animals. Claims limited to transgenic mice carrying a transgene construct of the type disclosed, wherein the mice exhibit the disclosed phenotype are appropriate.

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.
September 30, 1998

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